308-2023-03

OLANZAPINE FOR INJECTION

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OLANZAPINE FOR INJECTION safely and effectively. See full prescribing information for OLANZAPINE FOR INJECTION.

OLANZAPINE for injection, powder, for solution for intramuscular use

Initial U.S. Approval: 1996

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. olanzapine is not approved for the treatment of patients with dementia-related psychosis. (5.1, 8.5, 17)**

INDICATIONS AND USAGE

Olanzapine for injection is an atypical antipsychotic indicated:
- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
- Efficacy was established in three 1-day trials in adults. (14.3)

DOSAGE AND ADMINISTRATION

Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4)	IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max.3 doses 2-4 hrs apart)

Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.4)

DOSAGE FORMS AND STRENGTHS

- Intramuscular Injection: 10 mg vial. (3)

CONTRAINDICATIONS

- None with olanzapine monotherapy. (4)
- When using olanzapine in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

WARNINGS AND PRECAUTIONS

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):* Discontinue if DRESS is suspected. (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. (5.5)
  - *Hyperglycemia and Diabetes Mellitus:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.5)
  - *Dyslipidemia:* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.5)
  - *Weight Gain:* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.5)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.6)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including olanzapine. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of olanzapine should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Anticholinergic (antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. (5.14)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and at least twice that for placebo) associated with:

Combination of olanzapine and Lithium or Valproate:
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia. (6.1)

Olanzapine for Injection:
- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aspiro Pharma Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Pediatric Use:* Safety and effectiveness of olanzapine for injection in children < 13 years of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. olanzapine for injection is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.

1 INDICATIONS AND USAGE

1.4 Olanzapine for injection: Agitation Associated with Schizophrenia and Bipolar I Mania

Olanzapine for injection IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

2 DOSAGE AND ADMINISTRATION

2.4 Olanzapine for injection: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2 to 4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.7)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5 to 20 mg/day as soon as clinically appropriate.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of olanzapine for injection — Olanzapine for injection IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of olanzapine for injection IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. Olanzapine for injection IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose, mg Olanzapine	Volume of Injection, mL
10	Withdraw total contents of vial
7.5	1.5
5	1
2.5	0.5

Physical Incompatibility Information — Olanzapine for injection IntraMuscular should be reconstituted only with Sterile Water for Injection. Olanzapine for injection IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute olanzapine for injection IntraMuscular as this combination results in a delayed reconstitution time. Olanzapine for injection IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

3 DOSAGE FORMS AND STRENGTHS

Olanzapine for injection is available in 10 mg/ vial (1s).

4 CONTRAINDICATIONS

- None with olanzapine for injections monotherapy.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

5 WARNINGS AND PRECAUTIONS

5.1 Elderly Patients with Dementia-Related Psychosis

Increased Mortality — **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine for injection is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.**

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17)]*.

5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17)]*.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue olanzapine if DRESS is suspected *[see Patient Counseling Information (17)]*.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. Olanzapine's specific metabolic profile is presented below.

Hyperglycemia and Diabetes Mellitus

Healthcare providers should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100 to 126 mg/dL, nonfasting 140 to 200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug *[see Patient Counseling Information (17)]*.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N = 22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N = 19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥ 200 mg/dL, and/or a baseline fasting glucose level ≥ 126 mg/dL). Olanzapine-treated patients had a greater mean HbA_{1c} increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA_{1c} decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4 to 5 weeks), 6.1% of olanzapine-treated subjects (N = 855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N = 599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: N	Up to 12 weeks exposure: Patients	At least 48 weeks exposure: N	At least 48 weeks exposure: Patients
Fasting Glucose	Normal to High (< 100 mg/dL to ≥ 126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA[a]	NA[a]
	Borderline to High (≥ 100 mg/dL and < 126 mg/dL to ≥ 126 mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA[a]	NA[a]

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N = 487). In analyses of patients who completed 9 to 12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N = 121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

Table 3: Changes in Fasting Glucose Levels from Adolescent Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: N	Up to 12 weeks exposure: Patients	At least 24 weeks exposure: N	At least 24 weeks exposure: Patients
Fasting	Normal to High (< 100 mg/dL to ≥ 126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA[a]	NA[a]
Glucose	Borderline to High (≥ 100 mg/dL and < 126 mg/dL to ≥ 126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA[a]	NA[a]

[a] Not Applicable.

Dyslipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17)]*.

Clinically significant, and sometimes very high (> 500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4 to 6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in longterm studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: N	Up to 12 weeks exposure: Patients	At least 48 weeks exposure: N	At least 48 weeks exposure: Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6%	487	61.4%
		Placebo	402	26.1%	NA[a]	NA[a]
	Normal to High (< 150 mg/dL to ≥ 200 mg/dL)	Olanzapine	457	9.2%	293	32.4%
		Placebo	251	4.4%	NA[a]	NA[a]
	Borderline to High (≥ 150 mg/dL and < 200 mg/dL to ≥ 200 mg/dL)	Olanzapine	135	39.3%	75	70.7%
		Placebo	65	20.0%	NA[a]	NA[a]
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	745	21.6%	489	32.9%
		Placebo	402	9.5%	NA[a]	NA[a]
	Normal to High (< 200 mg/dL to ≥ 240 mg/dL)	Olanzapine	392	2.8%	283	14.8%
		Placebo	207	2.4%	NA[a]	NA[a]
	Borderline to High (≥ 200 mg/dL and < 240 mg/dL to ≥ 240 mg/dL)	Olanzapine	222	23.0%	125	55.2%
		Placebo	112	12.5%	NA[a]	NA[a]
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	536	23.7%	483	39.8%
		Placebo	304	14.1%	NA[a]	NA[a]
	Normal to High (< 100 mg/dL to ≥ 160 mg/dL)	Olanzapine	154	0%	123	7.3%
		Placebo	82	1.2%	NA[a]	NA[a]
	Borderline to High (≥ 100 mg/dL and < 160 mg/dL to ≥ 160 mg/dL)	Olanzapine	302	10.6%	284	31.0%
		Placebo	173	8.1%	NA[a]	NA[a]

[a] Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

Table 5: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure: N	Up to 6 weeks exposure: Patients	At least 24 weeks exposure: N	At least 24 weeks exposure: Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA[a]	NA[a]
	Normal to High (< 90 mg/dL to > 130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA[a]	NA[a]
	Borderline to High (≥ 90 mg/dL and ≤ 130 mg/dL to > 130 mg/dL)	Olanzapine	37	59.5%	31	64.5%
		Placebo	17	35.3%	NA[a]	NA[a]
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA[a]	NA[a]
	Normal to High (< 170 mg/dL to ≥ 200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA[a]	NA[a]
	Borderline to High (≥ 170 mg/dL and < 200 mg/dL to ≥ 200 mg/dL)	Olanzapine	36	38.9%	33	57.6%
		Placebo	13	7.7%	NA[a]	NA[a]
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA[a]	NA[a]
	Normal to High (< 110 mg/dL to ≥ 130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA[a]	NA[a]
	Borderline to High (≥ 110 mg/dL and < 130 mg/dL to ≥ 130 mg/dL)	Olanzapine	29	48.3%	21	47.6%
		Placebo	9	0%	NA[a]	NA[a]

[a] Not Applicable.

Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure to event of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N = 2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use in Adults

Amount Gained kg (lb)	6 Weeks (N = 7465) (%)	6 Months (N = 4162) (%)	12 Months (N = 1345) (%)	24 Months (N = 474) (%)	36 Months (N = 147) (%)
≤ 0	26.2	24.3	20.8	23.2	17.0
0 to ≤ 5 (0-11 lb)	57.0	36.0	26.0	23.4	25.2
> 5 to ≤ 10 (11-22 lb)	14.9	24.6	24.2	24.1	18.4
> 10 to ≤ 15 (22-33 lb)	1.8	10.9	14.9	11.4	17.0
> 15 to ≤ 20 (33-44 lb)	0.1	3.1	8.6	9.3	11.6
> 20 to ≤ 25 (44-55 lb)	0	0.9	3.3	5.1	4.1
> 25 to ≤ 30 (55-66 lb)	0	0.2	1.4	2.3	4.8
> 30 (> 66 lb)	0	0.1	0.8	1.2	2

Dose group differences with respect to weight gain have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N = 199), 20 (N = 200) and 40 (N = 200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

Table 7: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials

	Olanzapine-treated patients	Placebo-treated patients
Mean change in body weight from baseline (median exposure = 3 weeks)	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	40.6% (median exposure to 7% = 4 weeks)	9.8% (median exposure to 7% = 8 weeks)
Percentage of patients who gained at least 15% of baseline body weight	7.1% (median exposure to 15% = 19 weeks)	2.7% (median exposure to 15% = 8 weeks)

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N = 179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N = 106), overweight (N = 26) and obese (N = 17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

Table 8: Weight Gain with Olanzapine Use in Adolescents

Amount Gained kg (lb)	6 Weeks (N = 243) (%)	6 Months (N = 191) (%)
≤ 0	2.9	2.1
0 to ≤ 5 (0-11 lb)	47.3	24.6
> 5 to ≤ 10 (11-22 lb)	42.4	26.7
> 10 to ≤ 15 (22-33 lb)	5.8	22.0
> 15 to ≤ 20 (33-44 lb)	0.8	12.6
> 20 to ≤ 25 (44-55 lb)	0.8	9.4
> 25 to ≤ 30 (55-66 lb)	0	2.1
> 30 to ≤ 35 (66-77 lb)	0	0
> 35 to ≤ 40 (77-88 lb)	0	0
> 40 (> 88 lb)	0	0.5

5.6 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase.

However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

5.7 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α1-adrenergic antagonistic properties *[see Patient Counseling Information (17)]*.

From an analysis of the vital sign data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, orthostatic hypotension was recorded in ≥ 20% (1277/6030) of patients.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥ 30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2 to 3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression.

5.8 Falls

Olanzapine may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including olanzapine. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of olanzapine should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue olanzapine and have their WBC followed until recovery.

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17)]*.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17)]*.

5.14 Anticholinergic (antimuscarinic) Effects

Olanzapine exhibits *in vitro* muscarinic receptor affinity *[see Clinical Pharmacology 12.2]*. In premarketing clinical trials, Olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations, but Olanzapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. In post marketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications *[see Drug Interactions (7.1)]*.

5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events1 (2% [49/3240] of females), sexual function-related events[2] (2% [150/8136] of females and males), and breast-related events3 (0.7% [23/3240] of females, 0.2% [9/4896] of males).

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (1% [2/168] of females), sexual function-related events[2] (0.7% [3/454] of females and males), and breast-related events[3] (2% [3/168] of females, 2% [7/286] of males) *[see Use in Specific Populations (8.4)]*.

[1] Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea.

[2] Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction.

[3] Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder.

Dose group differences with respect to prolactin elevation have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N = 199), 20 (N = 200) and 40 (N = 200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of prolactin elevation > 24.2 ng/mL (female) or > 18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) indicated significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day.

5.16 Use in Combination with Lithium, or Valproate

When using olanzapine and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for lithium or valproate *[see Drug Interactions (7)]*.

5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

Clinical Trials in Adults

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 10,504 adult patients with approximately 4765 patient-years of exposure to olanzapine plus 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 additional patients from 88 oral olanzapine clinical trials as of December 31, 2001; (5) 1843 additional patients from 41 olanzapine clinical trials as of October 31, 2011; and (6) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. Also included below is information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing healthcare provider with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation - Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA

Adverse Reaction	Percentage of Patients Reporting Event: Olanzapine (N = 248)	Percentage of Patients Reporting Event: Placebo (N = 118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[a]	8	4
Akathisia	5	1

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)

Adverse Reaction	Percentage of Patients Reporting Event: Olanzapine (N = 125)	Percentage of Patients Reporting Event: Placebo (N = 129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short- Term, Placebo-Controlled Trials

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥ 2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo- Controlled Clinical Trials with Oral Olanzapine

Body System/Adverse Reaction	Percentage of Patients Reporting Event: Olanzapine (N = 532)	Percentage of Patients Reporting Event: Placebo (N = 294)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

Dose Dependency of Adverse Reactions

A dose group difference has been observed for fatigue, dizziness, weight gain and prolactin elevation. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N = 199), 20 (N = 200) and 40 (N = 200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) was observed with significant differences between 10 vs 40 and 20 vs 40 mg/day. The incidence of dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) was observed with significant differences between 20 vs 40 mg. Dose group differences were also noted for weight gain and prolactin elevation *[see Warnings and Precautions (5.5, 5.15)]*.

The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

Table 12: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo

Adverse Reaction	Placebo (N = 68)	Olanzapine 5 ± 2.5 mg/day (N = 65)	Olanzapine 10 ± 2.5 mg/day (N = 64)	Olanzapine 15 ± 2.5 mg/day (N = 69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

(Percentage of Patients Reporting Event)

Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥ 5% and at least twice placebo) were:

Table 13: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes) Percentage of Patients Reporting Event

Adverse Reaction	Percentage of Patients Reporting Event: Olanzapine with lithium or valproate (N = 229)	Percentage of Patients Reporting Event: Placebo with lithium or valproate (N = 115)
Dry mouth	32	9
Weight gain	26	7
Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2

Dimensions: 350 x 750 mm

Colour: Black

Adverse Reaction	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Amnesia	5	2
Paresthesia	5	2

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short- Term Trials of Olanzapine as Adjunct to Lithium or Valproate

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

Body System/Adverse Reaction	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea[a]	2	0
Vaginitis[a]	2	0

[a]Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection- Treated Patients in Short-Term, Placebo-Controlled Trials

Table 15 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5 to 10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

Table 15: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania

Body System/Adverse Reaction	Percentage of Patients Reporting Event	
	Olanzapine (N=415)	Placebo (N=150)
Body as a Whole		
Asthenia	2	1
Cardiovascular System		
Hypotension	2	0
Postural hypotension	1	0
Nervous System		
Somnolence	6	3
Dizziness	4	2
Tremor	1	0

Extrapyramidal Symptoms

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[a]	15	14	12	14
Akathisia[b]	23	16	19	27

[a] Percentage of patients with a Simpson-Angus Scale total score > 3.
[b]Percentage of patients with a Barnes Akathisia Scale global score ≥ 2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[a]	1	3	2	3
Parkinsonism events[b]	10	8	14	20
Akathisia events[c]	1	5	11	10
Dyskinetic events[d]	4	0	2	1
Residual events[e]	1	2	5	1
Any extrapyramidal event	16	15	25	32

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[c]Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[e]Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents

Categories[a]	Percentage of Patients Reporting Event	
	Placebo (N=89)	Olanzapine (N=179)
Dystonic events	0	1
Parkinsonism events	2	1
Akathisia events	4	6
Dyskinetic events	0	1
Nonspecific events	0	4
Any extrapyramidal event	6	10

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism[a]	0	0	0	0	3
Akathisia[b]	0	0	5	0	0

[a]Percentage of patients with a Simpson-Angus Scale total score > 3.
[b] Percentage of patients with a Barnes Akathisia Scale global score ≥ 2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

Table 20: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia

	Percentage of Patients Reporting Event				
	Placebo (N=45)	Olanzapine IM 2.5 mg (N=48)	Olanzapine IM 5 mg (N=45)	Olanzapine IM 7.5 mg (N=46)	Olanzapine IM 10 mg (N=46)
Dystonic events[a]	0	0	0	0	0
Parkinsonism events[b]	0	4	2	0	0
Akathisia events[c]	0	2	0	0	0
Dyskinetic events[d]	0	0	0	0	0
Residual events[e]	0	0	0	0	0
Any extrapyramidal events	0	4	2	0	0

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
e Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Dystonia, Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently ($< 1\%$) with olanzapine use.

Other Adverse Reactions

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

Cardiovascular System — *Infrequent:* cerebrovascular accident, vasodilatation.

Digestive System — *Infrequent:* abdominal distension, nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

Hemic and Lymphatic System — *Infrequent:* thrombocytopenia.

Metabolic and Nutritional Disorders — *Frequent:* alkaline phosphatase increased; *Infrequent:* bilirubinemia, hypoproteinemia.

Musculoskeletal System — *Rare:* osteoporosis.

Nervous System — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

Respiratory System — *Infrequent:* epistaxis; *Rare:* lung edema.

Skin and Appendages — *Infrequent:* alopecia.

Special Senses — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

Urogenital System — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

[1] These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.
[2]Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥ 2.5 mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

Body as a Whole — *Frequent:* injection site pain.

Cardiovascular System — *Infrequent:* syncope.

Digestive System — *Infrequent:* nausea.

Metabolic and Nutritional Disorders - *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥ 2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13 to 17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)

Adverse Reactions	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
	Olanzapine (N=72)	Placebo (N=35)	Olanzapine (N=107)	Placebo (N=54)
Sedation[a]	39	9	48	9
Weight increased	31	9	29	4
Headache	17	6	17	17
Increased appetite	17	9	29	4
Dizziness	8	3	7	2
Abdominal pain[b]	6	3	6	7
Pain in extremity	6	3	5	0
Fatigue	3	3	14	6
Dry mouth	4	0	7	0

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.
[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short- Term (3 to 6 weeks), Placebo-Controlled Trials

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥ 2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13 to 17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])

Adverse Reaction	Percentage of Patients Reporting Event	
	Olanzapine (N=179)	Placebo (N=89)
Sedation[a]	44	9
Weight increased	30	6
Increased appetite	24	6
Headache	17	12
Fatigue	9	4
Dizziness	7	2
Dry mouth	6	0
Pain in extremity	5	1
Constipation	4	0
Nasopharyngitis	4	2
Diarrhea	3	0
Restlessness	3	2
Liver enzymes increased[b]	8	1
Dyspepsia	3	1
Epistaxis	3	0
Respiratory tract infection[c]	3	2
Sinusitis	3	0
Arthralgia	2	0
Musculoskeletal stiffness	2	0

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.
[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.
[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes

Olanzapine Monotherapy in Adults: An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤ 90 IU/L, the incidence of ALT elevations to > 200 IU/L was 2% (50/2381). None of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from < 3 times the upper limit of normal [ULN] at baseline to ≥ 3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥ 5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to 0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, high GGT levels were recorded in $\geq 1\%$ (88/5245) of patients.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK. From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, elevated uric acid was recorded in $\geq 3\%$ (171/4641) of patients.

Olanzapine Monotherapy in Adolescents: In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT ($\geq$3X ULN in patients with ALT at baseline $<$3X ULN), (12% vs 2%); elevated AST (28% vs 4%); low total bilirubin (22% vs 7%); elevated GGT (10% vs 1%); and elevated prolactin (47% vs 7%).

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from < 3 times ULN at baseline to ≥ 3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. ALT elevations ≥ 5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.7)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of olanzapine. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to olanzapine therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), cholestatic or mixed liver injury, diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hepatitis, jaundice, neutropenia, pancreatitis, priapism, rash, restless legs syndrome, rhabdomyolysis, salivary hypersecretion, stuttering[1], and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥ 240 mg/dL and random triglyceride levels of ≥ 1000 mg/dL have been reported.

[1]Stuttering was only studied in oral and long acting injection (LAI) formulations.

7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity.

Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

Fluvoxamine: Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients, receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

Fluoxetine: Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the C_{max} and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Anticholinergic Drugs — Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. Olanzapine should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects *[see Warnings and Precautions (5.14)]*.

7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists - Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.7)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — *In vitro* studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

Biperiden — Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including olanzapine, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs, including olanzapine, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall available data from published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including olanzapine, during pregnancy *(see Clinical Considerations)*.

Olanzapine was not teratogenic when administered orally to pregnant rats and rabbits at doses that are 9- and 30-times the daily oral maximum recommended human dose (MRHD), based on mg/m[2] body surface area; some fetal toxicities were observed at these doses (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal adverse reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including olanzapine, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Placental passage has been reported in published study reports; however, the placental passage ratio was highly variable ranging between 7% to 167% at birth following exposure during pregnancy. The clinical relevance of this finding is unknown.

Published data from observational studies, birth registries, and case reports that have evaluated the use of atypical antipsychotics during pregnancy do not establish an increased risk of major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

Animal Data

In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the daily oral MRHD based on mg/m[2] body surface area, respectively), no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the daily oral MRHD based on mg/m[2] body surface area), and gestation was prolonged at 10 mg/kg/day (5 times the daily oral MRHD based on mg/m[2] body surface area). In an oral rabbit teratology study, fetal toxicity manifested as increased resorptions and decreased fetal weight, occurred at a maternally toxic dose of 30 mg/kg/day (30 times the daily oral MRHD based on mg/m[2] body surface area).

8.2 Lactation

Risk Summary

Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk *(see Clinical Considerations)*. There is no information on the effects of olanzapine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for olanzapine and any potential adverse effects on the breastfed child from olanzapine or from the mother's underlying condition.

Clinical Considerations

Infants exposed to olanzapine should be monitored for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of olanzapine (D_2 receptor antagonism), treatment with olanzapine may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.15)]*.

8.4 Pediatric Use

Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels *[see Warnings and Precautions (5.5, 5.15, 5.17) and Adverse Reactions (6.1)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and dyslipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.

Safety and effectiveness of olanzapine in children < 13 years of age have not been established *[see Patient Counseling Information (17)]*.

8.5 Geriatric Use

In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17)]*. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the daily oral MRHD (20 mg) and rhesus monkeys administered oral doses up to 8 times the daily oral MRHD based on mg/m[2] body surface area.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with $\geq 10\%$ incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

10.2 Management of Overdose

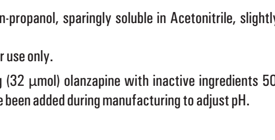
There is no specific antidote to an overdose of olanzapine The possibility of multiple drug involvement should be considered. Establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Contact a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222).

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the prescribing information for those products.

11 DESCRIPTION

Olanzapine is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.4. The chemical structure is:



Olanzapine is a yellow crystalline solid, soluble in n-propanol, sparingly soluble in Acetonitrile, slightly soluble in Methanol and in dehydrated alcohol and practically insoluble in water.

Olanzapine for injection is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of olanzapine, in the listed indications is unclear. However, the efficacy of olanzapine in schizophrenia could be mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism.

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ (Ki=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic M_{1-5} (K_i=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds with low affinity to $GABA_A$, BZD, and β-adrenergic receptors ($K_i > 10$ μM).

12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that olanzapine tablets and olanzapine orally disintegrating tablets dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. *In vitro* studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway *in vivo*, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration — olanzapine for injection results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

Specific Populations

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine.

The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥ 65 years) than in nonelderly subjects (< 65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — *In vivo* studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8 to 5 times the daily oral MRHD based on mg/m[2] body surface area) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06 to 2 times the daily oral MRHD based on mg/m[2] body surface area). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13 to 2 and 0.13 to 4 times the daily oral MRHD based on mg/m[2] body surface area, respectively).

The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice at 2 times the daily oral MRHD based on mg/m[2] body surface area. These tumors were not increased in another mouse study in females dosed up to 2 to 5 times the daily oral MRHD based on mg/m[2] body surface area; in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥ 2 mg/kg/day and in female rats dosed at ≥ 4 mg/kg/day (0.5 and 2 times the daily oral MRHD based on mg/m[2] body surface area, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.15)]*.

Mutagenesis — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, *in vivo* micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the daily oral MRHD based on mg/m[2] body surface area, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the daily oral MRHD based on mg/m[2] body surface area). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the daily oral MRHD based on mg/m[2] body surface area); therefore olanzapine may produce a delay in ovulation.

13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the daily oral MRHD based on mg/m[2] body surface area), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the daily oral MRHD based on mg/m[2] body surface area) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the daily oral MRHD based on mg/m[2] body surface area) for 3 months or 16 mg/kg (8 times the daily oral MRHD based on mg/m[2] body surface area) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

14 CLINICAL STUDIES

14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥ 14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor

impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥ 4 using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Olanzapine for Injection is a yellow color lyophilized cake or powder and is available as follows:

10 mg per vial:
Single-Dose Vial in a carton of 1 NDC 31722-308-01

16.2 Storage and Handling

Store olanzapine for injection vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted olanzapine for injection may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted olanzapine IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect olanzapine for injection from light, do not freeze.

17 PATIENT COUNSELING INFORMATION

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking olanzapine for injection as monotherapy. If you do not think you are getting better or have any concerns about your condition while taking olanzapine for injection, call your doctor.

Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with olanzapine for injection had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

Olanzapine for injection is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Neuroleptic Malignant Syndrome (NMS)

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine for injection. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Patients should be advised to report to their health care provider at the earliest onset of any signs and symptoms that may be associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.4)]*.

Hyperglycemia and Diabetes Mellitus

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking olanzapine for injection *[see Warnings and Precautions (5.5)]*.

Dyslipidemia

Patients should be counseled that dyslipidemia has occurred during treatment with olanzapine for injection. Patients should have their lipid profile monitored regularly *[see Warnings and Precautions (5.5)]*.

Weight Gain

Patients should be counseled that weight gain has occurred during treatment with olanzapine for injection. Patients should have their weight monitored regularly *[see Warnings and Precautions (5.5)]*.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine for injection, e.g., diazepam or alcohol *[see Warnings and Precautions (5.7) and Drug Interactions (7)]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heartbeat, or fainting.

Potential for Cognitive and Motor Impairment

Because olanzapine for injection has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine for injection therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see Warnings and Precautions (5.13)]*.

Concomitant Medication

Patients should be advised to inform their healthcare providers if they are taking, or plan to take, Symbyax. Patients should also be advised to inform their healthcare providers if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions *[see Drug Interactions (7)]*.

Alcohol

Patients should be advised to avoid alcohol while taking olanzapine for injection *[see Drug Interactions (7)]*.

Use in Specific Populations

Pregnancy — Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with olanzapine for injection. Advise patients that olanzapine may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate.

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to olanzapine during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation — Advise breastfeeding women using olanzapine for injection to monitor infants for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs *[see Use in Specific Populations (8.3)]*.

Infertility — Advise females of reproductive potential that olanzapine for injection may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Pediatric Use — Olanzapine for injection is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic aminotransferase levels. Patients should be counseled about the potential long-term risks associated with olanzapine for injection and advised that these risks may lead them to consider other drugs first. Safety and effectiveness of olanzapine for injection in patients under 13 years of age have not been established. Safety and efficacy of olanzapine for injection and fluoxetine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with bipolar I disorder. Safety and effectiveness of olanzapine for injection and fluoxetine in combination in patients < 10 years of age have not been established *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.4)]*.

Need for Comprehensive Treatment Program in Pediatric Patients

Olanzapine for injection is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder.

Effectiveness and safety of olanzapine for injection have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the healthcare provider's assessment of the chronicity and severity of the patient's symptoms.

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Revised: 03/2023